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EXAMINER

VENCI, DAVID J

ART UNIT PAPER NUMBER

1641

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/621,958

Applicant(s)

LOCKE ET AL.

Examiner

David J. Venci

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on December 2, 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-31 is/are pending in the application.
- 4a) Of the above claim(s) 28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-27 and 29-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-31 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 10/31/05.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 2, 2005, is entered. Applicants amend claims 1-9, 11-13, 15-21 and 23-29, and add new claims 30-31.

Currently, claims 1-27 and 29-31 are under examination. Claim 28 is directed to a non-elected invention and was withdrawn from consideration in the Office Action of December 28, 2004.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement filed October 31, 2005, fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document. Specifically, Examiner is unable to locate a copy of WO 2003/050544 in the application file. The information referenced in WO 2003/050544 has not been considered.

Claim Rejections - 35 USC § 101

Claims 27 and 30-31 are rejected under 35 U.S.C. 101 because the claimed recitation of a use results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

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Claim Rejections - 35 USC § 112 – first paragraph

Claims 1-27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Examiner is unable to locate in the specification the following claim limitations:

In claims 1-3, 24-27 and 29-31:

The object(s) consisting or comprising an "affinity group"

The object(s) and/or step(s) required for "use of an affinity group"

The negative limitation "without use of an affinity group"

The object(s) and/or step(s) required for labeling "without use of an affinity group"

In claims 1-3, 27 and 29-31:

The object(s) and/or step(s) required for satisfaction of the condition wherein "molecules are derivatized prior to analysis"

In claim 29:

A method for the quantitative analysis of two or more "derivatives"

Applicants are required to cancel the new matter in response to this Office Action.¹

¹ Applicants are advised that, upon cancellation of the new matter, Examiner may revert to rejection of the amended claims using prior grounds for rejection in view of *Aebersold et al.* (US 6,670,194), *Figely et al.* (US 2002/0076817) and *Vandekerckhove & Gevaert* (US 2004/0005633) as set forth in the prior Office Action.

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Claim Rejections - 35 USC § 112 – second paragraph

Claims 1-27 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specific claim rejections under 35 USC 112, second paragraph set forth, *infra*, are considered relevant to other claims not explicitly mentioned, as deemed reasonably appropriate.

In claims 1-3, 27 and 29-31, the passive voice recitation “the molecules are derivatized” is indefinite. The identity of object(s) and/or step(s), if any, required for performing derivatization is/are not clear. Whether the act or process of derivatization is completed or performed, or merely intended, is not clear.

In claims 1-3, 27 and 29-31, the recitation of “derivatized prior to analysis” is indefinite. The identity of object(s) and/or step(s) required for satisfaction of the condition wherein “molecules are derivatized prior to analysis” is not clear.

In claims 1-3, 24-27 and 29-31, the passive voice recitation “the reagents are labeled” is indefinite. The identity of object(s) and/or step(s), if any, required for performing labeling is/are not clear. The identity of the label(s) for labeling “the reagents” is not clear. Whether “the reagents” are labeled with “differential isotope labeled reagents” is not clear. The overall purpose of labeling “the reagents” with “differential isotope labeled reagents” is not clear.

In claims 1-3, 24-27 and 29-31, the recitation of “affinity group” is indefinite. The identity of object(s) consisting or comprising an “affinity group” is not clear.

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In claims 1-3, 24-27 and 29-31, the recitation of "use of an affinity group" is indefinite. The identity of object(s) and/or step(s) required for "use of an affinity group" is not clear. The identity of object(s) and/or step(s) required for labeling "without use of an affinity group" is not clear.

In claims 1-3, 24-27 and 29-31, the phrase "the reagents" lacks antecedent basis.

In claims 1-3, 24-27 and 29-31, the phrase "the molecules" lacks antecedent basis.

In claims 1 and 27, the prepositional phrase "with at least two differential isotope labeled reagents" is indefinite. The object(s) of said prepositional phrase is/are not clear. Whether said prepositional phrase modifies "reacting" and/or "molecules" and/or "sample" is not clear.

In claims 1, 3, 24, 26-27, 29 and 31, the recitation of "differential isotope labeled reagents" is indefinite. The number of chemically distinct reagents is not clear. The number of isotopically distinct reagents is not clear.

In claims 1 and 27, the recitation of the phrase "wherein the differential isotope labeled reagents result in differential isotope labeled derivatives" is indefinite. How one noun can "result" in another noun is not clear.

In claims 2 and 30, the prepositional phrase "with isotope labeled reagents" is indefinite. The object(s) of said prepositional phrase is/are not clear. Whether said prepositional phrase modifies "reacting" and/or "molecules" is not clear.

In claims 3 and 31, the prepositional phrase "with differential isotope labeled reagents" is indefinite. The object(s) of said prepositional phrase is/are not clear. Whether said prepositional phrase modifies "reacting" and/or "molecules" and/or "sample" is not clear.

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In claims 3, the recitation of the phrase "wherein the differential isotope labeled reagents result in a reductive alkylation" is indefinite. How one noun can "result" in another noun is not clear.

In claim 5, the recitation of "the step of reacting the molecules with differential isotope labeled reagents" lacks antecedent basis in claim 2.

In claim 15, the recitation of "the differential isotope labeled reagents" lacks antecedent basis in claim 2.

In claim 24, the prepositional phrase "with the molecules" is indefinite. The object(s) of said prepositional phrase is/are not clear. Whether said prepositional phrase modifies "reaction" and/or "reagents" is not clear.

In claims 25-26, the prepositional phrase "for quantitative analysis by mass spectroscopy" appears grammatically misplaced. The object(s) of said prepositional phrase is/are not clear.

In claims 25-26 and 29, the recitation of "the molecules" lacks antecedent basis.

In claim 25, the recitation of "to alkylamine derivatives" and "by isotopically labeled reagents" appear grammatically misplaced. The object(s) of each phrase is/are not clear.

In claim 26, the recitation of the phrase "by differential isotope labeled reagents" appears grammatically misplaced. The object(s) of the phrase is/are not clear.

In claims 27 and 30-31, the preamble recitation of "[u]se of a mass spectrometer" is indefinite. The field(s) of art encompassed by said "[u]se" is/are not clear. The term "use" is neither defined in Applicants' specification nor is the term applied to Applicants' invention in the context of a "[u]se of a

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mass spectrometer". Whether Applicants' "use" is capable of establishing a basis for distinguishing Applicants' invention over the prior art is not clear.

In claim 29, the prepositional phrase "with differential isotope labeled reagents" is indefinite. The object(s) of said prepositional phrase is/are not clear. Whether said prepositional phrase modifies "reacting" and/or "molecules" and/or "extracts" is not clear.

Claim Rejections - 35 USC § 102

Claims 2-6, 8-15, 17-23, 25-26 and 29-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Aebersold *et al.* (US 6,670,194).

Aebersold *et al.* teach a method for the quantitative analysis (see Title, "Quantitative Analysis") of a sample of molecules (see col. 11, lines 35-39, "two or more protein samples", lines 47-54, "cell homogenates; cell fractions; biological fluids..." etc.) having an amine (see col. 10, lines 30-41, "PRGs... include... those that react with amino groups") bearing an active hydrogen comprising the steps of:

reacting the molecules with isotope labeled reagents (see col. 11, lines 35-39, "the proteins in each sample are reacted with affinity tagging reagents which are substantially chemically identical but differentially isotopically labeled") resulting in the reductive alkylation of the amines (see col. 10, lines 50-52, "amino reactive groups include aldehydes... in the presence... of NaBH₄ or NaCNBH₄") to their alkylamine derivatives, such that the alkylamine derivatives are isotopically labeled (see Abstract, "The linker may be differentially isotopically labeled"), and

examining the derivative by mass spectrometry (see Abstract, "reaction products are characterized by mass spectrometric (MS) techniques").

Examiner posits that Aebersold *et al.* explicitly teach a reaction of aldehydes (belonging to the PRGs) and amino groups (belonging to sample proteins) in the presence of NaBH₄ or NaCNBH₄. Consequently, the claimed "amine bearing an active hydrogen" and "alkylamine derivatives" necessarily result from this teaching of Aebersold *et al.* and would be so recognized by persons of ordinary skill in the art.

With respect to claims 3 and 29, Aebersold *et al.* teach a method for the quantitative analysis of two or more samples (see col. 11, lines 35-39, "two or more protein samples", lines 47-54, "cell homogenates;

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cell fractions; biological fluids..." etc.). In addition, Aebersold *et al.* teach the step of combining the derivatized molecules (see col. 6, lines 2-3, "The treated samples are then combined").

With respect to claims 4 and 29, Aebersold *et al.* teach a method comprising an additional step of cleaving the derivatized molecules prior to examining by mass spectrometry (see col. 6, lines 3-4).

With respect to claim 5, Aebersold *et al.* teach a method comprising an additional step of denaturing the molecules prior to reacting with isotopically labeled reagents (see col. 12, line 4-6).

With respect to claim 6, Aebersold *et al.* teach a method wherein electrospray ionization is used (see col. 11, lines 58-59).

With respect to claims 8-9, 11 and 29, Aebersold *et al.* teach a method comprising an additional step of separating derivatized molecules by 1D gel electrophoresis, 2D gel electrophoresis, or HPLC before examining by mass spectrometry (see col. 36, lines 11-12).

With respect to claim 10, Aebersold *et al.* teach a method comprising an additional step of separating the fragments after cleaving (see col. 19, lines 41-43).

With respect to claims 12-14 and 29, Aebersold *et al.* teach a method comprising an additional step of analyzing the preparation by CID in MS/MS mode to sequence the molecule (see col. 36, lines 19-36).

With respect to claims 15 and 17, Aebersold *et al.* teach a method wherein the isotopically labeled reagents are an aldehyde and a sodium borohydride reducing agent (see col. 10, lines 50-52).

With respect to claims 18-19 and 29, Aebersold *et al.* teach a method wherein the sample proteins are extracted from cells (see col. 5, line 63, "cell or tissue lysates").

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With respect to claim 20, Aebersold *et al.* teach a method wherein the amines are lysine residues and N-terminal amino groups (see col. 18, lines 11-12).

With respect to claims 21-23, Aebersold *et al.* teach a method wherein an electrospray ionization ion trap spectrometer is used (see col. 22, lines 29-30).

With respect to claim 25, Aebersold *et al.* describe a preparation of a sample (see col. 11, lines 35-39, "two or more protein samples", lines 47-54, "cell homogenates; cell fractions; biological fluids..." etc.) comprising isotopically labeled derivatives (see Abstract, "The linker may be differentially isotopically labeled") having an amine (see col. 10, lines 30-41, "PRGs... include... those that react with amino groups") bearing an active hydrogen, resulting from the reductive alkylation of the amines (see col. 10, lines 50-52, "amino reactive groups include aldehydes... in the presence... of NaBH₄ or NaCNBH₄") to their alkylamine derivatives. The claimed "alkylamine derivatives" necessarily results from the aforementioned teaching of Aebersold *et al.* and would be so recognized by persons of ordinary skill in the art.

With respect to claim 27, Aebersold *et al.* describe a method comprising a mass spectrometer (see Abstract).

Claim Rejections - 35 USC § 103

Claims 1, 4-15, 17-24 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold *et al.* (US 6,670,194) in view of Figeys *et al.* (US 2002/0076817).

Aebersold *et al.* teach a method for the simultaneous (see col. 11, line 40, "The samples are combined and processed as one") quantitative analysis (see Title, "Quantitative Analysis") of at least three samples (see col. 11, lines 35-39, "two or more protein samples", lines 47-54, "cell homogenates; cell fractions; biological fluids..." etc.) comprising the steps of:

reacting each sample with differential isotope labeled reagents (see col. 11, lines 35-39, "the proteins in each sample are reacted with affinity tagging reagents which are substantially chemically identical but differentially isotopically labeled") wherein the reagents are labeled (see col. 11, lines 35-39, "affinity tagging reagents are... differentially isotopically labeled"),

combining the derivatives (see col. 6, lines 2-3, "The treated samples are then combined"), and

examining the derivatives by mass spectrometry (see Abstract, "reaction products are characterized by mass spectrometric (MS) techniques").

Aebersold *et al.* do not teach the step of "reacting the molecules of each sample with at least two differential isotope labeled reagents."

However, Figeys *et al.* teach the step of reacting each sample with two differential isotope labeled reagents (see Fig. 6, "O¹⁶-water" and "O¹⁸-water") (see Fig. 6, "Peptides mixture") in order to label individual samples with distinct isotope ratios (see para. [0010]).

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It would have been obvious for a person of ordinary skill in the art to modify the simultaneous quantitative method of Aebersold *et al.* with the use of two isotopically labeled reagents because Figeys *et al.* teach that labeling individual samples with distinct isotope ratios allows a convenient means for "sample tracking" which allows a peptide to be traced back to its sample source (see para. [0036]).

With respect to claim 4-6, 8-15, 17-23 and 27, see *supra*.

With respect to claim 7, Figeys *et al.* teach a method wherein ionspray is used (see para. [0055]).

With respect to claims 24, Figeys *et al.* teach the step of reacting each sample with two differential isotope labeled reagents (see Fig. 6, "O¹⁶-water" and "O¹⁸-water") (see Fig. 6, "Peptides mixture").

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold *et al.* (US 6,670,194) and Figeys *et al.* (US 2002/0076817) as applied to claims 1 and 15, and further in view of Vandekerckhove & Gevaert (US 2004/0005633).

Aebersold *et al.* and Figeys *et al.* teach a method for the simultaneous quantitative analysis of at least three samples as substantially described, *supra*, and incorporated herein.

Aebersold *et al.* and Figeys *et al.* do not teach a method wherein formaldehyde and acetaldehyde are used.

However, Vandekerckhove & Gevaert teach the use of deuterated formaldehyde and acetaldehyde (see para. [0107]) in order to induce a distinguishable mass shift in peptide analysis.

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It would have been obvious for a person of ordinary skill in the art to modify the method of Aebersold *et al.* and Figeys *et al.* with the use of formaldehyde and acetaldehyde because Vandekerckhove & Gevaert teach that such reactions are “known to proceed in mild conditions” and “may lead to the incorporation of a predictable number of deuterium atoms” (see para. [0107]).

Response to Arguments

In prior Office Action, claims 1-27 and 29 were rejected under 35 U.S.C. 102(e) or 35 U.S.C. 103(a) in view of various combinations of teachings of Aebersold *et al.* (US 6,670,194), Figeys *et al.* (US 2002/0076817) and Vandekerckhove & Gevaert (US 2004/0005633).

In response, Applicants amend independent claims 1-3, 24-27 and 29-31 to add the new limitation of reagents "labeled without use of an affinity group". Applicants attempt to distinguish their claimed invention from that of Aebersold *et al.* by alleging that Applicants' invention is "a one component system" that combines an isotope label group (L) with a covalent attachment group (A) into a single molecule (see Applicants' reply, paragraph bridging pp. 13-14), whereas Aebersold *et al.* describe a "multi-component" reagent (see Applicants' reply, p. 13, fifth paragraph). Finally, Applicants posit that the present invention "involves placement of deuterium and/or carbon-13 in methyl amine (N-(CH₃)₂ or N-(CD₃)₂)" (see Applicants' reply, p. 14, first full paragraph and paragraph bridging pp. 14-15).

Applicants' arguments have been carefully considered but are not persuasive.

Notwithstanding issues of new matter and indefiniteness, set forth *supra*, *Claim Rejections - 35 USC § 112 – first paragraph*, and *Claim Rejections - 35 USC § 112 – second paragraph*, respectively, Examiner interprets said reagent "labeled without use of an affinity group" as a reagent that is labeled with a label (L) without any intervening affinity group.

The new claim limitation of reagents "labeled without use of an affinity group" is not sufficient to overcome anticipation by Aebersold *et al.* because Aebersold *et al.* also describe an isotope labeled reagent (see col. 4, line 6, "A—L—PRG") wherein the reagent (PRG) is labeled with a label (L) without any intervening affinity group.

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Applicants attempt to distinguish their claimed invention from that of Aebersold *et al.* by alleging that Applicants' invention is "a one component system", whereas Aebersold *et al.* describe a "multi-component" reagent is not persuasive because Aebersold *et al.* also describe "a one component system" (see col. 4, line 6, "A—L—PRG") that combines an isotope label group (L) with a covalent attachment group (A) into a single molecule (A—L—PRG). The mere fact that Aebersold *et al.* characterize said single molecule using the alphanumeric symbols A—L—PRG does not detract from the reality that Aebersold *et al.* also describe "a one component system" (see col. 4, line 6, "A—L—PRG") that combines an isotope label group (L) with a covalent attachment group (A) into a single molecule (A—L—PRG).

Applicants' arguments directed to the position that the present invention "involves placement of deuterium and/or carbon-13 in methyl amine ($N-(CH_3)_2$ or $N-(CD_3)_2$ " is not persuasive because Applicants appear to rely upon limitations that do not appear in the rejected claims. Although claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

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Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
Examiner
Art Unit 1641

djv

Christopher L. Chin
CHRISTOPHER L. CHIN
PRIMARY EXAMINER
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3/3/06